REMARKS

Notes on the December 21, 2010 teleconference

First, Applicants wish to thank the Examiner for his patience and cooperation during the teleconference. The Applicants appreciate the time requirements of Examiners and understand that spending over ninety minutes on the teleconference was somewhat taxing of his schedule.

Prior to the teleconference, the Examiner was faxed an outline of Applicants' questions and comments on 2 pm December 17, 2010 to be better informed as to the Applicants' desired agenda. The content of the teleconference held December 21, 2010 was reviewed in Examiner's **Interview Summary** mailed December 27, 2010. Below are the topics discussed, the Examiner's description and Applicants' response to each in order.

(1) Examiner's topic description: Applicant argues nonobviousness in the Medford reference as it relates to NF-kB and hyperlipidemia in VCAM-1 expressing cells. Applicant goes into great detail about HUVEIHAEC cell models not synthesizing LDL. This is not persuasive because only the part in the background section of Medford regarding the link between NF-kB and hyperlipidemia, and that NAC is a NF-kB inhibitor, was only used in the rejection. Therefore, the arguments directed to the actual composition and methods taught by Medford and corresponding mechanism of action are basically irrelevant to what it was actually relied on for.

Applicants' response: A review of the HUVE/HAEC cell models was, in the opinion of the Applicants, essential to convey and understand the totally of the

teaching of Medford, which the Examiner is apparently ignoring when, in his own words, focusing on "***only the part in the background section of Medford regarding the link between NF-kB and hyperlipidemia***". As emphasized in the teleconference, a prior art ***reference must be considered in its entirety***, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Distilling an invention down to the "gist" or "thrust" of an invention disregards the requirement of analyzing the subject matter "as a whole." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

Applicant noted that in this case, it appears that the Examiner has distilled the teaching of Medford to the "grist" of a single sentence [C2, line 10; the only mention of hyperlipidemia] in the BACKGROUND and disregarded the requirement of analyzing the subject matter "as a whole" by dismissing the need to understand the cell models and response variables taught by Medford.

(2) Examiner's topic description: Applicant argues that previously submitted. Kleinveld reference, teaches that NAC acts as a pro-oxidant rather than an anti-oxidant, therefore does not lower LDL levels. Examiner will take a closer look and consider this evidence, however, this may or may not reflect the state of the art as it relates to NAC being used for the claimed methods.

Applicants' response: The Kleinveld reference discussed [Kleinveld, H. A., P. N. Demacker, et al. (1992). "Failure of N-acetylcysteine to reduce low-density lipoprotein oxidizability in healthy subjects." Eur J Clin Pharmacol **43**(6): 639-642] reported the clinical

effects of NAC, which the Examiner infers to have antioxidant properties, on the susceptibility of low-density lipoprotein to oxidation and on whole-blood glutathione concentrations. The susceptibility of low-density lipoprotein to oxidation was the same variable examined by Medford in vitro. In Kleinveld, NAC was given orally in a dosage of at 1.2 g per day for 4 weeks, followed by 2.4 g per day for a further two weeks. In the authors' words, "NAC had no effect on the susceptibility of LDL to oxidation. Concentrations of vitamin E in the serum and in low-density lipoprotein were not changed. Compared with controls the concentration of glutathione in N-acetylcysteine treated subjects was reduced (-48%) and the concentration of oxidized glutathione was higher (+80%). The GSH/GSSG-ratio, a marker of oxidative stress was 83% lower. The results do not support the supposed antioxidative action of N-acetylcysteine. It seems more likely that N-acetylcysteine acts as a pro-oxidant in the dosage used". Table 1 of the Kleinveld reference indicates no clinical effect of NAC on total cholesterol, LDL cholesterol, HDL cholesterol, or LDL cholesterol.

In reviewing these findings of Kleinveld, Applicant emphasized to the Examiner that prior to Medford it was known in the art that clinically NAC functions as a pro-oxidant relative to its ability to inhibit the oxidation of LDL or reduced serum lipids. Moreover as a result of clinical evidence to the contrary, Medford's in vitro teaching of the action of NAC was considered clinically irrelevant by those trained in the art.

(3) **Examiner's topic description:** Applicant argues against substituting the antioxidant, Coenzyme Q10 in McCleary, *for* NAC in Medford because

Coenzyme Q10 was not used for its antioxidant properties, but for facilitating respiratory chain function and hence augments the process of reverse electrion (*sic*) transport. Examiner will take a closer look and determine that this is not because of the properties of an antioxidant but limited to the Coenzyme Q10.

Applicants' response: CoQ10 is a fat-soluble, vitamin-like substance synthesized by all cells and is present in the mitochondria where it functions as a component of the electron transport chain and participates in aerobic cellular respiration generating energy in the form of ATP. Synthesis of CoQ10 by cells decreases with age and extreme physical activity. McCleary's use of CoQ10 as a dietary supplement is limited to "the facilitation of respiratory chain function and augmentation of the process of reverse electron transport, which plays a key role in the thermogenic effect produced by accelerated fatty acid oxidation" [McCleary **0037**].

Thus, the mitochondrial functioning of CoQ10 is obviously the intention of McCleary. The antioxidant effects of CoQ10 occur primarily in erythrocytes in the plasma, while the electron transport function of CoQ10 occurs in the mitochondria. Since erythrocytes do not contain mitochondria, McCleary teaches away from the use of CoQ10 as an antioxidant.

(4) Examiner's topic description: Applicant argues that McCleary uses not only Coenzyme Q10 but in combination with additional active agents, therefore not attributing the therapeutic effect to *only* Coenzyme Q10. This is not persuasive because the instant claims use the transitional phrase "comprising" so as to not

preclude additional active agents. Examiner suggested the term "consisting of' as an alternative.

Applicants' response: The Applicants' notes on the teleconference indicate that this topic concerned CLA as an active agent in the McCleary application and not Coenzyme Q10. The Applicant pointed out that the McCleary application does not utilize CLA alone, but rather required, at minimum four components, hydroxycitric acid, carnitine, biotin and a gluconeogenic substance **plus** CLA.

Unrelated to the open-ended language of the claims in the instant application, Applicants questioned the logic of concluding from McCleary that CLA alone is an active agent when it is not necessary in the McCleary formulation to induce nutrient partitioning. As taught by McCleary, CLA is obviously not an essential, active ingredient for reducing serum lipids.

Finally, Applicant indicated that an amendment to the term "consisting of" would be considered.

(5) Examiner's topic description: Applicant argues unexpected results in the combination of NAC and CLA for the methods of treating hyperlipidemia and lipodystrophy in a HIV infected patient and points to the Declaration filed on *10/27/08*. This is not persuasive because of several issues:

> 1) It is not clear if the data is unexpected or not because there is no directed comparison made to NAC alone or CLA alone, therefore it is not certain where the therapeutic activity lies.

Applicants' response: Applicant agreed with the inference of the Examiner and stated this information will be provided in an additional

Declaration.

> 2) The data is not commensurate with the scope of the claims. The data shows a reduction in LDL levels. However no data is given for treating lipodystrophy. Furthermore, there is no experimental conditions shown, such as dosages, which is not reflected of the instant claims, which also recite no specific dosage ranges.

Applicants' response: Again, Applicant agreed with the inference of the Examiner and stated this information will be provided in an additional Declaration.

> 3) Applicant claims that no direct comparison can be made with CLA because it is unethical to administer it to the patient population since it raises LDL levels. This is indirect evidence of unexpected results for the combination of CLA and NAC. This is not persuasive because the facts remain that no comparison is made with the combination of CLA and NAC. Applicant points to Larsen as a review article regarding the effects of CLA. Examiner will take a closer look at this to determine whether it is reflective of the state of the art.

Applicants' response: Examiner has made the point that in order to make a direct comparison CLA would have to be administered as a single agent to a subject with HIV-1. This point, however, is inconsistent with a previous statement by the Examiner in an Office Action in response to Applicant's July 9, 2007 communication. In that communication, the Examiner stated , "although the etiologies may be different, it is clear as cited in the prior art that both fat maldistribution and hyperlipidemia are common to HIV and AIDS patients. Applicant noted that Larsen had previously been submitted to the Examiner and gave a brief overview of the literature review conducted by Larsen on the clinical

effects of CLA [Larsen, T. M., Toubro, S., and Astrup, A. Efficacy and safety of dietary supplements containing CLA for the treatment of obesity: evidence from animal and human studies. *J Lipid Res* **2003**, *44*, 2234-41]. At the time of the claimed invention seven of eight published clinical studies (86%, a super-majority) indicated a lack of effect of CLA on lowering blood lipids. Another, more comprehensive review of clinical studies was published subsequent to the filing of the instant application [see Salas-Salvado et al. in (6)] that reported no positive clinical effects of CLA on serum lipids in healthy humans or patients with overweight, obesity, metabolic syndrome, or diabetes.

(6) Examiner's topic description: Finally, Examiner reminds Applicant that the instant obviousness rejection could have been formulated in many ways. The one used was for substituting one known antioxidant for another based on their functional equivalence. The other way could have been combining two compositions known for the same purpose, which is to treat hyperlipidemia.

Applicants' response: As noted previously in the teleconference, McCleary does not teach the use of CoQ10 as an antioxidant and prior to Medford, NAC was shown clinically to be a pro-oxidant with no ability to reduce low-density lipoprotein oxidizability at the doses suggested in the instant application. Thus, neither CoQ10 nor NAC could be considered antioxidants in the context of McCleary and Medford, respectively.

With respect to the treatment of hyperlipidemia with NAC or CLA, the Applicant first pointed out that the instant application discloses in paragraph [0045] that, "Neither NAC, ALA nor any other thiol-containing compound has

ever been reported to effectively modify fat maldistribution or reduce elevated serum lipids resulting from HIV/ART". Further, Kleinveld demonstrated no effect of NAC on serum lipid variables in healthy subjects. Later and prior to the filing of the instant application, McComsey et al. [McComsey, G., H. Southwell, et al. (2003). "Effect of antioxidants on glucose metabolism and plasma lipids in HIV-infected subjects with lipoatrophy." J Acquir Immune Defic Syndr 33(5): 605-607] reported no effect of NAC plus vitamins C and E on plasma lipids in HIV-infected subjects with lipoatrophy. No statistically significant differences ($p<0.05$) were noted in serum cholesterol, LDL cholesterol, HDL cholesterol or triglycerides. Fasting glucose, however, significantly increased along with a significant increase in homeostatic model assessment values, reflecting an increase in insulin resistance. Thus, in the patient population, NAC failed to reduce serum lipids and adversely affected serum glucose and insulin levels.

With regards to CLA, At the time of the claimed invention seven of eight published clinical studies (86%) indicated a lack of effect of CLA on lowering blood lipids [reviewed in Larsen, T. M., Toubro, S., and Astrup, A. Efficacy and safety of dietary supplements containing CLA for the treatment of obesity: evidence from animal and human studies. *J Lipid Res* **2003**, *44*, 2234-41]. The authors of this review concluded, "the evidence from human, short-term studies suggest that CLA supplementation **does not reduce body fat or increase fat-free mass.** There is evidence that CLA isomers sold as dietary supplements have marked biological effects, but there is accumulating evidence that the CLA t10,c12 isomer may adversely influence human health by **producing lipodystrophy** and insulin resistance."

A second, later and more inclusive meta-analysis of CLA effects in

humans [Salas-Salvado, J., F. Marquez-Sandoval, et al. (2006). "Conjugated linoleic acid intake in humans: a systematic review focusing on its effect on body composition, glucose, and lipid metabolism." Crit Rev Food Sci Nutr **46**(6): 479-488], including healthy humans or patients with overweight, obesity, metabolic syndrome, or diabetes, concluded, "there is not enough evidence to show that conjugated linoleic acid has an effect on weight and body composition in humans. However, some of these studies have observed that the administration of various CLA isomers has adverse effects on lipid profile (it decreases HDL cholesterol concentration and increases Lp(a) circulating levels), glucose metabolism (glycemia, insulinemia or insulin sensitivity), lipid oxidation, inflammation, or endothelial function. . Of the 21 studies reviewed with information on lipid profiles, 15 indicated no effect (15/21), while six reported an adverse effect (6/21) of CLA. Thus, the preponderance of clinical evidence (86% in one study and 100%) supports the conclusion that CLA alone is not an effective treatment for hyperlipidemia.

Office Action11/15/10

Status of the Application

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/8/10 has been entered. Claim(s) 1-40 are pending. Claim(s) 1-20, 25-27, 30-31, 36-38 have been withdrawn. Claim(s) 21 and 32 have been amended.

Response to Examiner's Arguments of 11/15/10

Claim Rejections· 35 USC § 103

CoQ10 and NAC as functionally equivalent antioxidants

Examiner's comment (page 4, paragraph 2) - McCleary teach a nutritional supplement composition comprising conjugated linoleic acid and the antioxidant, coenzyme Q10, for modulating nutrient partitioning in a human (abstract).

Applicant response – McCleary does not disclose coenzyme Q10 (CoQ10) as an antioxidant in the abstract or anywhere else in the application. Rather, McCleary's use of CoQ10 as a dietary supplement is limited to "the facilitation of respiratory chain function and augmentation of the process of reverse electron transport, which plays a key role in the thermogenic effect produced by accelerated fatty acid oxidation" [McCleary, **0037**]. Again, in [McCleary, **0041**] CoQ10 is described useful for an "insulin sensitizing effect". This proposed use of CoQ10 in McCleary is supported by a large body of research demonstrating the role of CoQ10 in aberrant mitochondrial functioning and mutation in diabetes and insulin action [Kishi, T., H. Kishi, et al. (1976). "Bioenergetics in clinical medicine. XI. Studies on coenzyme Q and diabetes mellitus." J Med 7(3-4): 307-321; Silvestre-Aillaud, P., D. BenDahan, et al. (1995). "Could coenzyme Q10 and L-carnitine be a treatment for diabetes secondary to 3243 mutation of mtDNA?" Diabetologia **38**(12): 1485-1486; Suzuki, Y., H. Kadowaki, et al. (1995). "Insulin edema in diabetes mellitus associated with the 3243 mitochondrial tRNA(Leu(UUR)) mutation; case reports." Diabetes Res Clin Pract **29**(2): 137-142; Andersen, C. B., J. E. Henriksen, et al. (1997). "The effect of coenzyme Q10 on blood glucose and insulin requirement in patients with insulin dependent diabetes mellitus." Mol Aspects Med **18 Suppl**: S307-309; Suzuki, Y., M. Taniyama, et al. (1997). "Diabetes mellitus associated with 3243 mitochondrial tRNA(Leu(UUR))

mutation: clinical features and coenzyme Q10 treatment." Mol Aspects Med **18 Suppl**: S181-188; Suzuki, S., Y. Hinokio, et al. (1998). "The effects of coenzyme Q10 treatment on maternally inherited diabetes mellitus and deafness, and mitochondrial DNA 3243 (A to G) mutation." Diabetologia **41**(5): 584-588].

Thus, improved mitochondrial functioning of CoQ10 is obviously the intention of McCleary. The antioxidant effects of CoQ10 occur primarily in erythrocytes in the plasma, while the electron transport function of CoQ10 occurs in the mitochondria. Since erythrocytes do not contain mitochondria, McCleary teaches the use of CoQ10 to improve mitochondrial function and away from the use of CoQ10 as an antioxidant.

Examiner's comment (page 4, paragraph 3) - Medford et al. teach that activation of the transcriptional regulatory factor, NF-kB, is linked to hyperlipidemia. Importantly, activation of NF-kB can be inhibited by antioxidants such as N-acetylcysteine (col. 2, lines 6-14).

Applicant response – Medford discloses a method for assessing the ability of a compound to inhibit the "modification of low-density lipoprotein (LDL) into oxidatively modified LDL (ox-LDL) by reactive oxygen species". NAC was one of eight compounds tested by Medford for this capacity. Prior to Medford, Kleinveld [Kleinveld, H. A., P. N. Demacker, et al. (1992). "Failure of N-acetylcysteine to reduce low-density lipoprotein oxidizability in healthy subjects." Eur J Clin Pharmacol **43**(6): 639-642] reported the clinical effects of NAC on the susceptibility of low-density lipoprotein to oxidation (ox-LDL), the same variable examined by Medford in vitro. Kleinveld states, "NAC had no effect on the susceptibility of LDL to oxidation. Concentrations of vitamin E in the serum and in low-density

lipoprotein were not changed. The results do not support the supposed antioxidative action of N-acetylcysteine. It seems more likely that N-acetylcysteine acts as a pro-oxidant in the dosage used". Further, Table 1 of the Kleinveld reference shows no clinical effect of NAC on total cholesterol, LDL cholesterol, HDL cholesterol, or LDL cholesterol. Later and prior to the filing of the instant application, McComsey et al. [McComsey, G., H. Southwell, et al. (2003). "Effect of antioxidants on glucose metabolism and plasma lipids in HIV-infected subjects with lipoatrophy." J Acquir Immune Defic Syndr **33**(5): 605-607] reported no effect of NAC plus vitamins C and E on plasma lipids in HIV-infected subjects with lipoatrophy. No statistically significant differences ($p<0.05$) were noted in serum cholesterol, LDL cholesterol, HDL cholesterol or triglycerides. Fasting glucose, however, significantly increased along with a significant increase in homeostatic model assessment values, reflecting an increase in insulin resistance. Thus, in the patient population, NAC failed to reduce serum lipids and adversely affected serum glucose and insulin levels.

Therefore, prior to Medford and the filing of the instant application, it was known in the art that clinically NAC functions as a pro-oxidant relative to its ability to inhibit the oxidation of LDL or reduced serum lipids. Moreover as a result of evidence to the contrary, Medford's in vitro teaching of the action of NAC was considered clinically irrelevant by those trained in the art. This inference does not address the validity of Medford, as its teachings are limited to an in vitro assessment and do not necessarily translate to the clinical setting. Nevertheless, the clinical finding of Kleinveld in 1992 and McComsey et al in 2003 make it clear that NAC does not function as an anti-oxidant for the purpose

of reducing ox-LDL or serum lipids.

Examiner's comment (page 5, paragraph 1) - It would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have substituted coenzyme Q10 in the composition as taught by McCleary with N-acetylcysteine as taught by Medford.

A person of ordinary skill in the art would have been motivated to make this substitution because: (1) of the functional equivalence of both coenzyme Q10 and N-acetylcysteine as well-known antioxidants; and (2) both McCleary and Medford are aimed at treating hyperlipidemia. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in treating hyperlipidemia with a composition comprising a conjugated linoleic acid and the antioxidant, N-acetylcysteine.

Applicant response – As discussed above, (1) CoQ10 was not used for its anti-oxidant properties and it had been shown clinically that NAC did not inhibit ox-LDL or reduce serum lipids and demonstrated pro-oxidant effects when administered for these purposes; and (2) Medford's teaching was limited to in vitro studies and clinical evidence with NAC developed prior to and following Medford did not substantiate the potential for NAC proposed in the teaching.

Because CoQ10 was not used for its antioxidant properties in McCleary and NAC had been clinically demonstrated not to have anti-oxidant properties when used for hyperlipidemia or lipoatrophy, it would ***not*** have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have substituted coenzyme Q10 in the composition as taught by

McCleary with NAC as taught by Medford.

Therefore, one of ordinary skill in the art would not have had a reasonable expectation of success in treating a patient with hyperlipidemia coincident with subcutaneous fat loss and body wasting resulting from anti-retroviral treatment from an HIV-1 infection by administering a composition comprising a conjugated linoleic acid and N-acetylcysteine.

Examiner's comment (page 8, paragraphs 1 and 2) - Applicant argues that NF-kB is not linked to hyperlipidemia. Applicant goes on to explain a detailed mechanism of action involving VCAM-1 and LDL that somehow suggests that NF-kB is not linked to hyperlipidemia.

Applicant's view of the mechanism of action goes against the teaching of Medford, therefore considered an invalid interpretation of the reference. Applicant is reminded that the standard for obviousness is not absolute but a reasonable expectation of success.

Applicant response – The Applicant, based upon more than 30 years of research in cell culture, including the model employed by Medford, is well-versed in the concepts proposed by Medford. Much of the information for this response has been presented previously in the notes of the teleconference and will not be repeated. Moreover, in light of the clinical teachings of Kleinveld in 1992 and McComsey èt al in 2003 it was clear prior to the filing of the instant application that NAC did not function as an anti-oxidant for the purpose of reducing ox-LDL, serum lipids or modifying body composition.

Examiner's comment (page 8, paragraphs 3 and 4) - Applicant argues that

CLA is not known to treat hyperlipidemia. While McCleary teaches a combination comprising CLA for the treatment of hyperlipidemia, at the time of the claimed invention seven of eight published clinical studies indicated a lack of effect of CLA on lowering blood lipids.

This is not persuasive because these clinical studies appear not to be conclusive because no long-term studies were investigated. In fact, one of the seven appears to support the teachings of the McCleary reference. Nonetheless, Examiner does not view the eight published clinical studies as the state of the art regarding CLA's effect on blood lipids since it is in direct contradiction to the teachings of the McCleary reference.

Applicant response – As discussed previously, at the time of the claimed invention seven of eight published clinical studies (86%) indicated a lack of effect of CLA on lowering blood lipids [reviewed in Larsen, T. M., Toubro, S., and Astrup, A. Efficacy and safety of dietary supplements containing CLA for the treatment of obesity: evidence from animal and human studies. *J Lipid Res* **2003**, *44*, 2234-41]. The authors of this review concluded, "the evidence from human, short-term studies suggest that CLA supplementation **does not reduce body fat or increase fat-free mass.** There is evidence that CLA isomers sold as dietary supplements have marked biological effects, but there is accumulating evidence that the CLA t10,c12 isomer may adversely influence human health by **producing lipodystrophy** and insulin resistance" .

While the Examiner, "does not view the eight published clinical studies as the state of the art regarding CLA's effect on blood lipids since it is in direct contradiction to the teachings of the McCleary reference", the Examiner is

reminded that the McCleary reference claims a formulation and the cited review focused on CLA as a single, active ingredient. The McCleary application does not utilize CLA alone, but rather requires, at minimum four components including hydroxycitric acid, carnitine, biotin and a gluconeogenic substance **plus** CLA. Further, in McCleary CLA is not an essential component of the nutrient partitioning composition. If CLA were capable of affecting blood lipids alone, why does McCleary teach the need for a mandatory, additional four components? Obviously, CLA does not function to affect nutrient partitioning as a single agent. In this regard the teaching of McCleary and the review of CLA's effect on blood lipids are consistent.

Thus, the preponderance of clinical evidence (86%) supports the conclusion that CLA alone is not an effective treatment for hyperlipidemia or redistribution of body fat. The Examiner has previously rejected this argument stating, "This is not persuasive because these clinical studies appear not to be conclusive because no long-term studies were investigated. In fact, one of the seven appears to support the teachings of the McCleary reference." The argument that no long-term studies were conducted in specious when considering that there is less than a 15% probability of success, what research group would decided to do a long-term study?

Having been reminded that the standard for obviousness is not absolute but a reasonable expectation of success, the Applicants offer the lack of any longer-term studies as evidence for "no reasonable expectation of success". While admittedly subjective, the greater than 86% probability of failure described by the

reviews that have been published on the ability of CLA to positively affect serum lipids or modify body composition clearly does not support a preponderance of evidence standard or reasonable expectation of success.

Examiner's comment (page 9) - The Babish Declaration #3 under 37 CFR 1.132 filed 3/8/10 is insufficient to overcome the rejection of claims 21-24,28-29,32-35,39-40 based upon McCleary (US Patent Application *200210132219* A1) and Medford et al. (US Patent 5,750,351) in view of Applicant's admission of the prior art.

The Declaration seems make the case that CoQ10 and NAC are not functionally equivalent as antioxidants. The Declaration provides data in Exhibits B and C that show antioxidant activity for NAC, but no activity for CoQ10 when using various cell lines including the ones in Medford. This is not persuasive because Applicant is reminded that both CoQ10 and NAC are well known antioxidants.

Applicant response – While much of this material has been addressed previously, several points will be made in response to the Examiner's comments. As well established in prior art, the ability of any compound to function as an antioxidant is dependent upon the redox environment of the compound. A compound functioning as an antioxidant in one environment can be a pro-oxidant in another. In this regard, the clinical findings of Kleinveld in 1992 and McComsey et al in 2003 make it clear that NAC does not function as an anti-oxidant for the purpose of reducing ox-LDL or serum lipids.

Examiner's comment (page 9) - Applicant cannot argue that that one does not

possess antioxidant properties, otherwise why are they called "antioxidants" in the cited prior art?

Applicant response – As stated previously, CoQ10 is not termed an antioxidant in McCleary and teaching of Medford is limited to in vitro studies.

Examiner's comment (page 9) - Moreover, the data reflected in Exhibits Band C are limited to the very small amounts used in the study and the specific cell lines. A much broader study involving a wide range of amounts for both CoQ10 and NAC would be more convincing.

Therefore, a definitive conclusion cannot be said that that the antioxidant, CoQ10, does not have antioxidant properties.

Applicant response – The submitted data demonstrated the functional inequality of NAC and CoQ10 in the very cell lines used by Medford prior to the filing of the instant application. Concentrations tested were the highest possible relative to solubility and physiological meaning. Significantly, these data substantiate the in vitro work of Medford with NAC. The Applicants were, however, aware that NAC alone could not modify HAART-induced hyperlipidemia or lipoatrophy based upon published, peer-reviewed clinical trials and stated so in their application. From these studies, the Applicants were further aware that NAC and CoQ10 were not interchangeable antioxidants in the Medford model. Finally, the Applicants question the need for additional studies in other cell lines.

In summary, the information available to the Applicants in the scientific literature or generated in their laboratory prior to the filing of the instant

application removed any motivation to substitute NAC for CoQ10.

Examiner's comment (page 9, paragraph 4) Regarding the establishment of unexpected results, a few notable principles are well settled. It is applicant's burden to explain any proffered data and establish how any results therein should be taken to be unexpected and significant.

Applicant response – Applicants have filed an affidavit concurrent with this reply providing clear and convincing evidence of an unexpected benefit to the target population.

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

The requested declaration under 37 CFR § 1.132 to compare the claimed subject matter with the closet prior art in order to effectively to rebut a *prima facie* case of obviousness is enclosed. The declaration also explains how the results presented should be taken to be unexpected and significant.

During the teleconference described above, the Examiner made the point that in order to make a direct comparison CLA would have to be administered as a single agent to a subject with HIV-1. This point, however, is inconsistent with a previous statement by the Examiner in an Office Action in response to Applicant's July 9, 2007 communication. In that communication, the Examiner stated, "although the etiologies may be different, it is clear as cited in the prior art that both fat maldistribution and hyperlipidemia are common to HIV and AIDS patients". Therefore, clinical inoperability of CLA in the conditions of fat maldistribution and hyperlipidemia should be supported by subjects exhibiting

those conditions whether or not they are infected with the HIV-1 virus or not, as the etiologies may be different the manifestations are common.

As can be seen in the 2/14/11 Babish Declaration, sections 7.1.1 through 7.1.5 support the inoperability of the prior art for CLA in subjects manifesting hyperlipidemia, metabolic syndrome, type 2 diabetes and fat maldistribution (obesity) and NAC in HIV-infected subjects with lipodystrophy.

Taken together these references indicate that the use of CLA or NAC in the disclosed patient population would be expected, by one of ordinary skill in the art, to be potentially harmful; and any beneficial effect of CLA either alone or in a combination with NAC in the patient population would be unexpected and provide a significant, unfulfilled need in the patient population.

CLAIM AMMENDMENTS

Applicants have amended Claim 21 to read: A method for treating, or normalizing subcutaneous fat loss resulting from anti-retroviral treatment of HIV-1 infection in a subject in need thereof ~~comprising~~ consisting of administering to said subject a pharmaceutically effective dose of ~~a~~ conjugated ~~fatty~~ linoleic acid in combination with a pharmacologically effective dose of N-acetylcysteine ~~in a ratio of about 14:1 to 1:14,~~ and non-active ingredients including flavors and coloring agents, emulsifiers, preservatives and a pharmaceutically acceptable carrier in concert with anti-retroviral therapies.

Applicants have amended Claim 32 to read: A method for treating or normalizing hyperlipidemia coincident with subcutaneous fat loss and body wasting resulting from anti-retroviral treatment of HIV-1 infection in a subject in

need thereof ~~comprising~~ consisting of administering to said subject a pharmaceutically effective dose of ~~a~~ conjugated ~~fatty~~ linoleic acid in combination with a pharmacologically effective dose of N-acetylcysteine ~~in a ratio of about 14:1 to 1:14~~ and non-active ingredients including flavors and coloring agents, emulsifiers, preservatives and a pharmaceutically acceptable carrier in concert with anti-retroviral drug therapies.

SUMMARY

In summary, Applicant's present a review of the three basic criteria that must be met in order to establishing a *prima facie* case of obvious along with a summation of their previous responses:

(A) THERE MUST BE SOME SUGGESTION OR MOTIVATION, EITHER IN THE REFERENCES THEMSELVES OR IN THE KNOWLEDGE GENERALLY AVAILABLE TO ONE OF ORDINARY SKILL IN THE ART, TO MODIFY THE REFERENCE TEACHINGS.

1. There was no suggestion or motivation for the Applicants to combine the teaching of McCleary with the that of Medford and substitute NAC for coenzyme Q10 in combination with CLA for the treating or normalizing hyperlipidemia coincident with subcutaneous fat loss and body wasting resulting from anti-retroviral treatment of HIV-1 infection in a subject by administering CLA and NAC for the following reasons.

i. The prior art generated in the Applicants' own laboratory taught against the functional equivalence of NAC and coenzyme Q10 in the Medford cell model.

ii. The prior art disclosed the ***clinical*** failure of NAC to prevent the formation of ox-LDL from LDL.

iii. It was known at the time of the instant invention, that ***clinical*** use of NAC and antioxidants increased plasma glucose and insulin, and had no effect on plasma lipids in HIV-infected subjects with lipodystrophy while receiving anti-retroviral therapy.

iv. The prior art disclosed NAC is a pro-oxidant when administered to HIV-subjects with lipodystrophy.

v. In McCleary CoQ10 is not used as an antioxidant; rather it is used to facilitate respiratory chain function and augmentation of the process of reverse electron transport. Thus, the mitochondrial functioning capacity of CoQ10 was obviously the intention of McCleary. The antioxidant effects of CoQ10 occur primarily in erythrocytes in the plasma, while the electron transport function of CoQ10 occurs in the mitochondria. Since erythrocytes do not contain mitochondria, McCleary teaches away from the use of CoQ10 as an antioxidant.

(B) THERE MUST BE A REASONABLE EXPECTATION OF SUCCESS.

1. At the time of the claimed invention, a person of ordinary skill in the art would not have had a reasonable expectation of success to substitute NAC for coenzyme Q10 in combination with CLA for the treating or normalizing hyperlipidemia coincident with subcutaneous fat loss and body wasting resulting from anti-retroviral treatment of HIV-1 infection in a subject by administering triglyceride of CLA and NAC for the following reasons:

i. At the time of the claimed invention, a clinical trail had established that NAC did not inhibit the formation of ox-LDL and functioned as a pro-oxidant at the doses suggested in the instant application.

ii. At the time of the claimed invention, it was known that clinical use of NAC and antioxidants increased plasma glucose and insulin, and had no effect on plasma lipids in HIV-infected subjects with lipodystrophy while receiving anti-retroviral therapy.

iii. The use of CLA or NAC in the disclosed patient population would be expected, by one of ordinary skill in the art, to be potentially harmful; and any beneficial effect of CLA either alone or in a combination with NAC in the patient population would be unexpected and provide a significant, unfulfilled need in the patient population.

(C) FINALLY, THE PRIOR ART REFERENCES WHEN COMBINED MUST TEACH OR SUGGEST ALL THE CLAIM LIMITATIONS.

1. The prior art reference of McCleary combined with the that of Medford do not teach or suggest the treatment of subcutaneous fat loss resulting from anti-retroviral treatment of HIV-1 infection in a subject in need thereof with a formulation consisting of conjugated linoleic acid, N-acetylcysteine, and non-active ingredients including flavors and coloring agents, emulsifiers, preservatives and a pharmaceutically acceptable carrier in concert with anti-retroviral therapies.

2. The prior art reference of McCleary combined with the that of Medford do not teach or suggest the treatment of hyperlipidemia coincident

with subcutaneous fat loss and body wasting resulting from anti-retroviral treatment of HIV-1 infection in a subject in need thereof with a formulation consisting of conjugated linoleic acid, N-acetylcysteine, and non-active ingredients including flavors and coloring agents, emulsifiers, preservatives and a pharmaceutically acceptable carrier in concert with anti-retroviral therapies.

In view of the foregoing, the Applicants assert that Claims 21 and 32-32 of the present application present allowable subject matter and the allowance thereof are requested. If any impediment to the allowance of these claims remains after consideration of the present amendment and above remarks, and such impediment could be removed during a telephone interview, the Examiner is invited to telephone Dr. John G. Babish so that such issues may be resolved as expeditiously as possible.

Dated this 14th day of February 2011.

Respectfully submitted,
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